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10/534,955	02/06/2006	Gerd Haberhausen	21518-US	2633

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EXAMINER	
HINES, JANA A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/534,955	Applicant(s) HABERHAUSEN ET AL.	
	Examiner JaNa Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. The finality of the Office action mailed December 24, 2008 is hereby withdrawn in view of the new ground of rejection set forth below.

Amendment Entry

2. The amendments filed February 24, 2009 have been entered. Claims 6-7 and 10 are cancelled. Claims 1- and 8-9 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendment:

a) The rejection of claim 10 under 35 U.S.C. 102(b) as being anticipated by Jannes et al., (WO 96/00298);

b) The rejection of claims 1-6 and 8-9 under 35 U.S.C. 103(a) as being unpatentable over Jannes et al., (WO 96/00298) in view of de Silva et al., (Biochemica. 1998. No. 2:12-15); and

c) The new matter rejection of claims 1-5, and 8-10 under 35 U.S.C. 112, first paragraph.

Double Patenting

4. The examiner acknowledges applicants consideration of filing terminal disclaimers with respect to provisional obviousness-type double patenting rejections over application 10/534,915 and 10/534,319. However, the provisional obviousness-type double patenting rejections over claims 1, 2, 4, 6, 8 and 9 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/534,915 and 10/532,319 are maintained.

Response to Arguments

5. Applicant's arguments with respect to claims 1-5 and 8-9 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cockerill et al (US 7,074,598 B2 [11 July 2006; filed 25 September 2002]) in view of Jannes et al., (WO 96/00298).

The claims are drawn to a method for identification of a pathogenic Gram positive bacterium or a subset of pathogenic gram positive bacteria from a predetermined group of pathogenic Gram positive bacteria in a clinical sample comprising: a) providing said clinical sample containing at least partially purified nucleic acid, b) subjecting said clinical sample to at least one amplification step and at least one detection step in one reaction vessel, said steps comprising: ba) at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising at least 20 nucleotides of the 16S/23S Spacer region from a predetermined sub-group of pathogenic Gram positive bacteria to which said Gram positive bacterium or subset of pathogenic Gram positive bacteria belong, bb) at least one internal control template, and bc) at least one hybridization reagent capable of detecting said pre-selected nucleic acid sequence from said predetermined sub-group of pathogenic Gram positive bacteria, further comprising bca) monitoring hybridization of said hybridization reagent

at a pre-selected temperature, said hybridization being indicative for the presence in said clinical sample of at least one species contained in said predetermined sub-group, and bcb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for the presence of at least the species of said pathogenic Gram positive bacterium or said subset of pathogenic Gram positive bacteria, wherein said pathogenic Gram positive bacterium or subset of pathogenic Gram positive bacteria is identified based on the results of the monitoring steps in bca) and bcb).

Cockerill et al., disclose methods of detecting vancomycin-resistant *Enterococci* in biological samples, which methods employ real time PCR (col. 1, line 27-col. 2, line 14; col. 5, lines 3-34; and col. 11, line 34-col. 14, line 55). Cockerill et al., disclose the analysis by their methods of samples including clinical sample such as anal or peri-rectal swabs, stool samples, blood, and body fluids (col. 2, lines 66-67). Further, in detecting and determining the type of vancomycin-resistant *Enterococci* present in such samples, Cockerill et al., achieve the objective of "detecting the presence of a bacterial pathogen in a clinical sample". Cockerill et al., disclose the analysis of both samples and nucleic acids extracted therefrom, including total RNA or DNA extracted from clinical samples (col. 9, lines 16-30). Cockerill et al., disclose real-time PCR that is monitored by analysis of hybridization probe melting temperatures, allowing the identity of the specific target sequences present to be both detected and quantitated (col. 12, line 59-col. 14, line 55). Cockerill et al., also disclose that that samples with positive signals at melting temperatures corresponding to the various positive controls employed allow determination of the presence of the target sequence indicated by the

corresponding internal controls (col. 20, lines 27-40). Cockerill et al., teach plasmid controls can be amplified internally such as within each biological sample (col. 13, lines 13-17). Cockerill et al disclose the analysis of *Enterococci*. Cockerill et al., teach the use of FRET (col. 9-11, lines 58-17). Cockerill et al., teach two probes, each containing a fluorescent moiety can hybridize to an amplification product at particular positions determined by complementarity of the probes to the vancomycin-resistant *Enterococci* target nucleic acid sequence and upon hybridization of the probes to the amplification product a FRET signal is generated (col. 9-10, lines 65-5). Example 3 teach the amplification and detection steps occurring in one reaction vessel (col. 18, lines 20-50). However, Cockerill et al do not teach methods in which the 16S/23S spacer region is employed as an amplification/detection target.

Jannes et al., teach a method of amplification and detection of one or several pathogenic organisms, specifically bacteria, through the detection of the rRNA spacer region (abstract). Jannes teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising: a) at least partially purifying nucleic acid from a clinical sample (Example 3, p. 78-83; alternatively, see Example 4, p. 84-86, p. 85 where clinical isolates were tested, see Table 7), b) subjecting said clinical specimen to at least one amplification step and at least one detection step, comprising: ba) an amplification step using at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising region from a predetermined sub-group of pathogenic Gram-positive bacteria to which said gram positive pathogenic bacteria belong (p. 82-83 or p. 85, bb)

a detection step using at least one hybridization reagent capable of detecting a pre-selected nucleic acid sequence region from said sub-group of pathogens (p. 82-83 or p. 85, where clinical isolates were amplified using biotinylated primers and hybridized to 16s/23s rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or 7 for hybridization results), said detection step bb) further comprising: bba) monitoring hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for the presence in the sample of at least one species contained in the sub-group (p. 82-83 or p. 85, where clinical isolates were amplified and hybridized to 16S/23S rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or Table 7, where a variety of pathogens within a group were distinguished), and identifying the organisms or subset of organisms based on the results of step bb). Jannes et al., teach the identification of *Listeria, Mycobacterium, Streptococcus, Staphylococcus aureus* (page 4, lines 11-24 and page 5, lines 2-3). Jannes et al., teach an embodiment wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, Example 3, p. 78, where *Listeria*, a gram positive organism is detected. Jannes et al., teach the use of a predetermined group including *Staphylococcus aureus, Streptococcus pneumoniae* (page 24, lines 1-7; page 25, lines 1-7). Table 6 shows predetermined groups having *Enterococcus faecalis* and *Enterococcus faecium*. Example 9 and Table 9 show taxa tested.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cockerill et al so as to have adapted the method to permit rapid species identification of *Enterococci*

Staphylococcus and *Streptococcus* via real time, specific PCR amplification of 16S/23S spacer sequences, either in addition to or instead of the *van* target sequences exemplified by Cockerill et al, in order to detect of one or several pathogenic bacteria, through the detection of the rRNA spacer region. An ordinary artisan would have been motivated to have made such a modification for the advantage of and in order to have achieved the predictable result of determining bacterial species responsible for a particular infection, either instead of or in addition to determining whether the bacteria was vancomycin resistant. Furthermore, all of the claimed elements were known and disclosed by Cockerill et al., and Jannes et al., where one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

7. Claims 1-5 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitt et al (Journal of Clinical Pathology, vol. 53, pages 71-75, 2000) in view of Ke et al. (Clin. Chem. 2000. Vol.46(3):324-331).

Pitt et al., teach molecular techniques used in clinical bacteriology, and the advantages of real-time PCR techniques (page 71). Pitt et al., teach the use of gene targets with are universal or species specific such as the 16S and 23S rRNA sequences and the detection of the presence of the species by PCR or hybridization with specific probes (page 71). Pitt et al., teach the universal probes for Gram positive bacteria (page

71). Pitt et al., teach commercially available single tube assays using hybridization techniques for detection are mainstream wherein the goal is single test to detect the widest range of resistance mechanisms (page 72). Pitt et al., teach that real-time PCR is a powerful technique combining sample amplification and analysis in a single reaction tube (page 73). Pitt et al., teach that real-time PCR detection methods are generally dependent upon liquid phase oligonucleotide probe hybridization which results in changes in the levels of fluorescence as the target amplicon accumulates during cycling (page 73) . Pitt et al., teach that all of the probe systems rely on the same physical principal known as FRET (page 74). Pitt et al., teach that an example is the SYBRGreenI/Cy5 system, which acts as the photon donor when it is bound to double stranded DNA and the Cy5 acts as the acceptor (page 74). Pitt et al., state that the number of photons produced by FRET is increased when DNA bound SYBRGreen and Cy5 are brought into close proximity as occurs when probe binds to its target sequence within the amplicon (page 74). Pitt et al., teach that real time PCR is advantages in that the potential for contamination of the laboratory and amplicons released during analysis is effectively eliminated since the tube are not open post-PCR (page 74). Pitt et al., teach the use of real time PCR machines such as LightCyclers™ to speed up the process greatly by combining amplification with a means for detection of the specific product by fluorescence so that both steps occur conveniently in a single reaction tube (page 73). Pitt et al., further teach that the use of real-time instruments greatly simplifies the quantitation of initial PCR target DNA levels (page 74). Pitt et al, further state that the fluorescence is monitored during each temperature cycle so that products

accumulation can be detected in its exponential phase (see 73 to 74, entire section entitled "Real Time PCR"). However Pitt et al., do not specifically discloses the use of internal controls.

Ke et al., teach the development of real-time PCR assays for the rapid detection of *Streptococci*. Ke et al., teach the adaptation of PCR primers with LightCyclers^{TM} using two fluorogenic adjacent hybridization probes (abstract). Ke et al., teach the construction of internal controls wherein the plasmid was optimized to permit amplification of the internal control product without detrimental effect on the amplification (page 325, col. 2). Ke et al., teach the concomitant amplification of the internal control which allowed verification of the efficiency of the PCR to ensure that there was no significant PCR inhibition by the test sample (page 327, col.1). Ke et al., teach that use of internal control allows validation of the amplification primers, simplification of the assay and prevention of potential detrimental competition between different PCR primer pairs (page 328-329, col. 2-1). Ke et al., teach that it is critical that there be no significant competitive interference from the internal control template in order to minimize a decrease in the sensitivity of the assay. Ke et al., teach that the because amplification and detection occur in the same reaction vessel and no post amplification sample transfer is needed, the LightCyclers^{TM} platform greatly reduces the risk of carryover, making it more suitable for use in routine clinical settings (page 330, col.1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to incorporate internal controls into the reaction vessel as

taught by Ke et al., into the identification method as taught by Pitt et al., in order to allow the internal control to validate the amplification primers while simplifying the assay. One of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Pitt et al., and incorporate the use of internal controls as taught by Ke et al., to arrive at the claimed invention with in order to provide development of real-time PCR assays for the rapid detection of Gram positive bacteria using two fluorogenic adjacent hybridization probes wherein the inclusion of internal controls optimized amplification without detrimental effect of decreasing the sensitivity of the assay. Furthermore, all of the claimed elements were known and disclosed by Pitt et al., and Ke et al, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention including the prevention of potential detrimental competition between different PCR primer pairs and eliminating the need for post amplification transfers.

8. Claims 1-5 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jannes et al., (WO 96/00298) and de Silva et al., (Biochemica. 1998. No. 2:12-15) in view of Ke et al. (Clin. Chem. 2000. Vol.46(3):324-331).

Jannes et al., has been discussed above however, Jannes et al., do not explicitly teach internal controls or temperature dependence of hybridization being monitored as indicative for at least the species of said pathogen.

De Silva et al., teach rapid genotyping and quantification on the LightCycler™ with hybridization probes using two hybridization probes that recognize adjacent internal sequences within target DNA sequences (abstract). De Silva et al., teach amplification and analysis require no sample handling after loading (page 12). de Silva et al., teach an embodiment comprising bcb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for at least the species of said pathogen (p. 14, Figures 3 and 5, where an example of monitoring temperature dependence of hybridization is depicted). de Silva et al., teach fluorescence monitoring of amplification using hybridization probes based upon signals generated by FRET offers advantages over other techniques because its linear responses over a large dynamic range (page 12). Once amplification and FRET occur, a melting curve is generated that allows for rapid genotyping (page 13). de Silva et al., teach continuous fluorescence monitoring of the reaction as temperature is raised (page 13). de Silva et al., teach that changes can be easily distinguished suggesting that the fluorescence method is suitable for all single base mismatches (page 13). de Silva et al., teach a sensitive system that allows a single template copy to be distinguished and fluorescent probes that obtain the strongest signals (page 14-15).

Ke et al., has been discussed above as teaching that use of internal control allows validation of the amplification primers, simplification of the assay and prevention

of potential detrimental competition between different PCR primer pairs wherein amplification and detection occur in the same reaction vessel.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to extend the methods as taught by Jannes et al., and incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva et al., in order to arrive have the advantages over other techniques because of FRETs linear responses over a large dynamic range while further including internal controls as taught by Ke et al., which simplify the assay and allow for validation of the amplification primers. One of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Jannes et al., and incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva to arrive at the claimed invention with in order to provide a more sensitive system having stronger signals. Furthermore, no more than routine skill would have been required to incorporate the methods of Jannes et al., and de Silva et al., to further incorporate the use of internal controls as taught by Ke et al., to arrive at the claimed invention with in order to provide development of real-time PCR assays for the rapid detection of Gram positive bacteria using two fluorogenic adjacent hybridization probes wherein the inclusion of internal controls optimized amplification without detrimental effect of decreasing the sensitivity of the assay. Finally, all of the claimed elements were known and disclosed by Jannes et al., de Silva et al, and Ke et al., therefore one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions,

and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645